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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,049	01/17/2006	Kristen E. Belmonte	PU60400	6150

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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
03/07/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/565,049	BELMONTE ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4 and 6-16 are pending in the application.

2. This application is a national stage of PCT/US2004/023042 filed on July 16, 2004 which claims priority to U.S. Provisional Application No. 60/488,061 filed July 17, 2003.

Request for Continued Examination

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 30, 2008 has been entered.

Response to Arguments

4. Applicant's arguments filed on January 30, 2008 have been fully considered but they are not persuasive. The applicant has claimed that the examiner has improperly made the rejection final and asked for a withdrawal of the finality. This request is denied. The rejection was entirely proper. The claims were amended after the first action, to recite pharmaceutical compositions only (while the previous claims were drawn to compounds). Should the examiner apply new art or augment the rejection with new references it is entirely appropriate. The references were in fact not some newly discovered art of Zirkle but rather both were cited on the IDS or 892 and are drawn to the same compounds. While some compounds may be present in the U.S. patent and not the journal article and vice versa, the instantly claimed compounds are clearly present in both U.S. patent 2,800,478 and *Journal of Medicinal & Pharmaceutical*

Chemistry, **1962**, *5*, 341-356, as evidenced by their description (they have the same melting point in both references and the same chemical structure). Again it is worth pointing out that the Zirkle teaching is the basis of the specification. What is remarkable is the argument that the teachings of Zirkle are not enabling, or different in their degree of enablement with respect to the compound that formed the basis of the rejection. Is the suggestion that one teaching is better than the other? Is the applicant suggesting that the earlier Zirkle was a better Zirkle, perhaps a more competent chemist that the latter Zirkle? There is no evidence that the early Zirkle was a superior Zirkle or a different Zirkle. Is the applicant suggesting that the Zirkle of the U.S. patent 2,800,478 and *Journal of Medicinal & Pharmaceutical Chemistry*, **1962**, *5*, 341-356 are in fact different Zirkle's? If there are two Zirkle's, it is just as reasonable to assume that the early Zirkle of U.S. patent 2,800,478 was the unskilled chemist and the Zirkle of *Journal of Medicinal & Pharmaceutical Chemistry* was the dexterous chemist as it is to assume the converse. Since the applicant has argued the converse, namely that the latter Zirkle was the unskilled practitioner, and it has been established that both propositions have an equal probability or improbability of being true, in the absence of probative evidence of the inferiority of one Zirkle over the other this becomes an argument that the specification is not enabled. The applicant should clearly admit on the record that the specification is non-enabled or present evidence of two different Zirkle's or the inferiority of either the younger Zirkle or the elder Zirkle.

Regardless of the applicant's position on the nature of these references, the examiner believes that there was only one Zirkle, the Zirkle who worked at Smith-Kline French, filed and received the U.S. patent and later published the results in the *Journal of Medicinal & Pharmaceutical Chemistry*, **1962**, *5*, 341-356. These results show how to make the compound,

and disclose the pharmacological activity of these compounds, namely that they inhibit acetylcholine induced response with activity similar to atropine. For these reasons claims to the composition were clearly anticipated. The recitation of intended use carries no patentable weight in claims for compositions of matter see *Union Oil Co. of California v. Atlantic Richfield Co.* 54 USPQ2d 1227 where "composition claims cannot, as the appellant refiners argue, embrace only certain uses of that composition. (citing In Re Spada) Otherwise these composition claims would mutate into method claims." Ethanol or ethanol/ether solutions can be inhaled. As can solid material. Nonetheless the examiner now applies a 103 rejection based on other teachings.

While the applicant has provided no actual information, but only prophetic assays, the examiner will maintain the enablement rejection for the reasons of record. This rejection will be maintained unless the applicant will state on the record that performing the prophetic assays of the specification is routine experimentation. The entire specification is speculation. To clarify the rejection of claim 6, which is drawn to "inhibiting the binding of acetylcholine to a[sic] acetylcholine receptor in a mammal in need thereof", was made because we do not know what mammals need this compound since no physiological outcome has been associated with administering these compounds, thus no veterinarian or physician would know which mammals should receive this material and the method cannot be practiced.

Objections

5. Claim 6 is objected to for improper grammar. After the words "binding of acetylcholine to" the word "a" should be replaced with "an".

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zirkle et. al. U.S. patent 2,800,478 OR Zirkle et. al. *Journal of Medicinal & Pharmaceutical Chemistry*, **1962**, *5*, 341-356. in view of Gillett, M. K.; Snashall, P. D. "Measurement of pharmacological antagonism produced by atropine in bronchi of normal and asthmatic subjects" *European Respiratory Journal* **1988**, 1(1), 27-33 and U. S. Patent 6,608,055. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

Zirkle et. al. U.S. patent 2,800,478 teaches the compounds of the current invention as a solid manipulated in air and thus inherently containing air (the composition would be composed of particles of the compound in a composition with air and such a composition would inhalable). In this publication the compound of claim 3, (3-endo)-3-(2,2-diphenylethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide (applicant's name), Registry #: 106655-97-4 is synthesized and evaluated for its anticholinergic activity. The examiner believes this reference to be clearly

enabled. Clearly solid compounds, ethanol or ethanol ether solutions of these compounds can be inhaled. They were hydrogenated in ethanol, and also recrystallized form ethanol or ethanol/ether).

nium hydroxide solution. The ether layer is separated and the solvent evaporated to give 1,1-diphenyl-2-(3-tropane)ethylene as a white crystalline solid which melts at 109.5–110° C. after recrystallization from acetone.

1,1-diphenyl-2-(3-tropane)ethane.—10 grams of 1,1-diphenyl-2-(3-tropane)ethylene dissolved in ethanol is hydrogenated over Raney nickel at 500 p. s. i. and 60° C. until hydrogen absorption ceases. After removal of the catalyst and evaporation of the solvent 1,1-diphenyl-2-(3-tropane)ethane is obtained as a colorless oil.

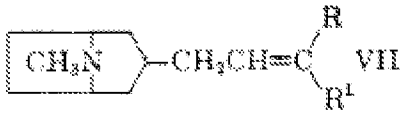
The hydrochloride of the base, formed in ethereal hydrogen chloride solution, melts at 244–245° C. after recrystallization from a mixture of ethanol and ether.

1,1-diphenyl-2-(3-tropane)ethane methobromide.—By allowing a mixture of 1 gram of 1,1-diphenyl-2-(3-tropane)ethane and excess methylbromide dissolved in acetone to stand at room temperature for several hours, the methobromide salt is obtained as white crystals. The product, after recrystallization from a mixture of ethanol and ether, melts at 257–258° C.

1,1-diphenyl-2-(3-tropane)ethane metho-p-toluenesulfonate.—An acetone solution of one gram of 1,1-diphenyl-2-(3-tropane)ethane and excess methyl p-toluenesulfonate is heated at reflux temperature for five minutes. By addition of ether to the cooled solution the quaternary ammonium salt is precipitated as a white solid.

1,1-diphenyl-2-(3-tropane)ethane maleate.—By adding 0.12 g. of maleic acid to 0.30 g. of 1,1-diphenyl-2-(3-tropane)ethane dissolved in ethanol and evapoating the resulting solution to dryness in vacuo the maleate salt of the base is obtained.

Zirkle et. al. *Journal of Medicinal & Pharmaceutical Chemistry*, **1962**, *5*, 341-356 teaches as per pg. 349 paragraph 2 “The tropane alkane derivatives listed in Table IV were obtained by reduction of the corresponding olefins. Olefin VII was hydrogenated smoothly over Raney nickel at room temperature and 4.2 kg./cm hydrogen pressure……” Compound VII is the olefin:



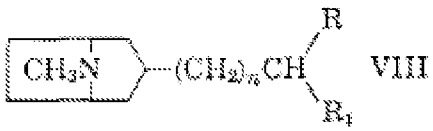
VII

The relative portion of Table IV is reproduced here:

TABLE IV
3-SUBSTITUTED TROPANE ALKANES

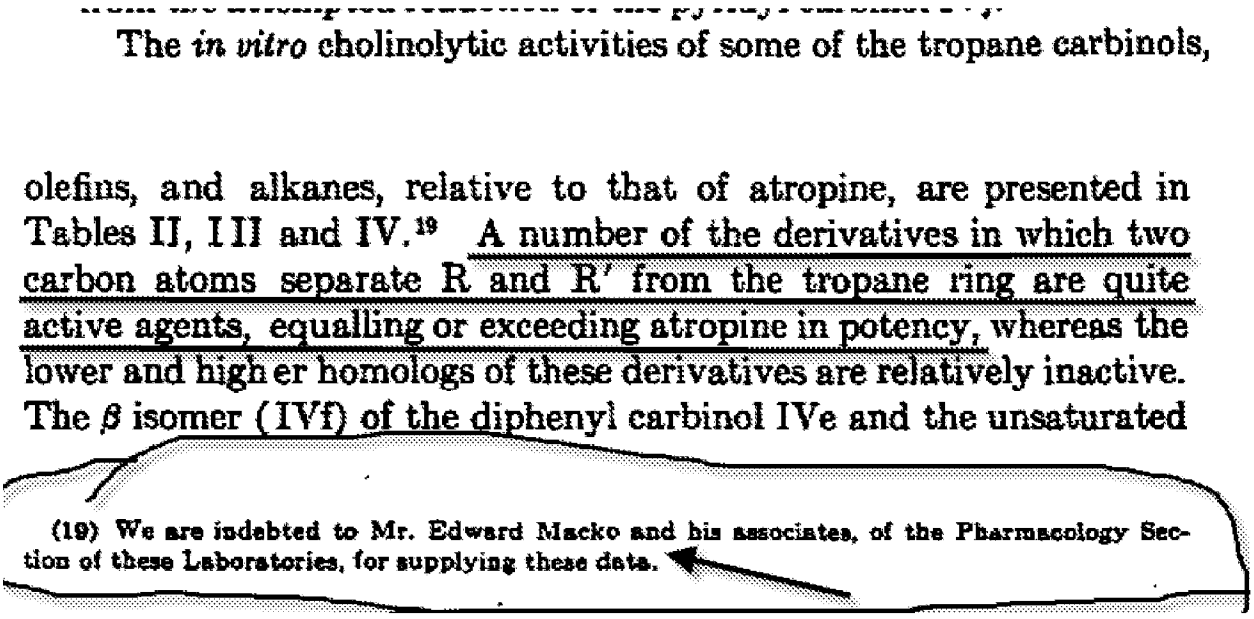
Compound[a] No.	n	R	R¹	Config.	Salt	M.p., °C.	Solvent[d]
a	0	CH_3	CH_3	α[b]	...	...[c]	
					HCl	194–196	AB
					CH_3I	224–226	AB
b	0	C_6H_5	C_6H_5	α[b]	...	70–72	
					HCl	>310	AB
					CH_3Br	277–278	CA
c	1	C_6H_5	C_6H_5	α	HCl	244–245	AB
					CH_3Br	257–258	AB

It would appear that structure VIII was omitted from the top heading of Table IV.



VIII

Clearly these compounds are simply salts of the free amines, and this operation (mixing with acid or alkyl halide/crystallizing) was not discussed in detail. It is relatively common for scientists not to discuss trivial procedures that all in the art are aware. This reaction of amines has been known for a very long time, for example a 1924 introductory lab text where the hydrochloride salt of methyl amine is prepared (Norris, James F. *Experimental Organic Chemistry* McGraw-Hill: New York, 1924, pgs. 88-91.) Furthermore it is apparent that the reference inherently discloses solid material (which is inhalable and exists as a composition with air at atmospheric pressure). An excerpt from pgs. 352-353 are shown below:



The *in vitro* cholinolytic activities of some of the tropane carbinols, olefins, and alkanes, relative to that of atropine, are presented in Tables II, III and IV.[19] A number of the derivatives in which two carbon atoms separate R and R′ from the tropane ring are quite active agents, equalling or exceeding atropine in potency, whereas the lower and higher homologs of these derivatives are relatively inactive. The β isomer (IVf) of the diphenyl carbinol IVe and the unsaturated

(19) We are indebted to Mr. Edward Macko and his associates, of the Pharmacology Section of these Laboratories, for supplying these data.

While it is not clear what tissues were involved they were clearly administered in some fashion (composition or powder).

Regardless, since the compounds of the instant case are anticholinergics and atropine (an anticholinergic) has been used in inhalation formulations as taught by Gillett, M. K.; Snashall, P. D. "Measurement of pharmacological antagonism produced by atropine in bronchi of normal and asthmatic subjects" *European Respiratory Journal* **1988**, 1(1), 27-33 and clearly the preparation

of an inhalable formulation of these compounds is trivial undertaking as per U.S. patent 6,608,055 (see columns 9 & 10) it would be obvious to prepare a different formulation (a dry powder with additives) and test them as anticholinergics as per the teaching of Zirkle.

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According to another aspect, the present invention relates to the use of crystalline anhydrous tiotropium bromide as a medicament in the light of the pharmaceutical efficacy of the anhydrous form according to the invention. To prepare a medicament which can be inhaled, particularly an inhalable powder, which contains the anhydrous, crystalline tiotropium bromide described by the present invention, methods known from the prior art may be used. In this respect, reference is made, for example, to the teaching of DE-A-179 22 07. Accordingly a further aspect of the present invention relates to inhalable powders characterised in that they contain anhydrous, crystalline tiotropium bromide.

Because of the potency of tiotropium bromide, the powders for inhalation mentioned above preferably contain, in addition to the active substance, the following physiologically acceptable excipients. The following physiologically acceptable excipients may be used, for example: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, sucrose, maltose), oligo- and polysaccharides (e.g. dextrane), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred.

Within the scope of the inhalable powders according to the invention the excipients which are characterised in that they contain anhydrous crystalline tiotropium bromide have a maximum average particle size of up to 250 μm, preferably between 10 and 150 μm, most preferably between 15 and 80 μm. It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 to 9 μm to the excipients mentioned above. These finer excipients are also selected from the group of possible excipients listed hereinbefore.

Preferred inhalable powders containing the tiotropium bromide anhydrate according to the invention are characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of from 17 to 50 μm, more preferably 20 to 30 μm, and finer excipient with an average particle size of 2 to 8 μm, more preferably 3 to 7 μm. The term average particle size here denotes the 50% value from the volume distribution measured with a laser diffractometer by the dry dispersion method. Inhalable powders wherein the proportion of finer excipient in the total quantity of excipient is 3 to 15%, more preferably 5 to 10%, are preferred.

One possible method of preparing these inhalable powders which are preferred according to the invention is discussed in more detail hereinafter.

After the starting materials have been weighed out, first the excipient mixture is prepared from the defined fractions of the coarser excipient and finer excipient. Then the inhalable powders according to the invention are prepared from the excipient mixture and the active substance. If the inhalable powder is to be administered by means of inhalettes in suitable inhalers, the preparation of the inhalable powders is followed by the production of the capsules containing the powder.

The inhalable powders according to the invention are prepared by mixing the coarser excipient fractions with the finer excipient fractions and subsequently mixing the resulting excipient mixtures with the active substance.

In order to prepare the excipient mixture the coarser and finer excipient fractions are placed in a suitable mixing container. The two components are preferably added through a screening granulator with a mesh size of 0.1 to 2 mm, most preferably 0.3 to 1 mm, even more preferably 0.3 to 0.6 mm. Preferably the coarser excipient is put in first and then the finer excipient fraction is added to the mixing container. In this mixing process the two components are preferably added batchwise, with half the coarser excipient being put in first followed by finer and coarser excipient added alternately. It is particularly preferable when preparing the excipient mixture to screen the two components in alternate layers. Preferably this screening of the two components takes place in 15 to 45, more preferably in 20 to 40 alternate layers. The mixing of the two excipients may take place while the two components are being added. However, it is preferably not done until the layers of ingredients have been added.

After the preparation of the excipient mixture, this and the active substance are placed in a suitable mixing container. The active substance used has an average particle size of 0.5 to 10 μm, preferably 1 to 6 μm, more preferably 2 to 5 μm. The two components are preferably added through a screening granulator with a mesh size of 0.1 to 2 mm, most preferably 0.3 to 1 mm, even more preferably 0.3 to 0.6 mm. Preferably the excipient mixture is put in first and then the active substance is added to the mixing container. It is particularly preferable when preparing the excipient mixture to screen the two components in alternate layers. Preferably this screening of the two components takes place in 25 to 65, more preferably in 30 to 60 alternate layers. The mixing of the excipient mixture with the active substance may take place while the two components are being added. However, it is preferably not done until the layers of ingredients have been added.

The powder mixture thus obtained may optionally be passed through a screening granulator once again or several times more and then subjected to another mixing operation each time.

The inhalable powders obtained by the above method preferably contain about 0.001 to 2% tiotropium bromide in admixture with a physiologically acceptable excipient. Preferred are inhalable powders which contain 0.04 to 0.8% of tiotropium bromide in admixture with a physiologically acceptable excipient, characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of 15 to 80 μm and finer excipient with an average particle size of 1 to 9 μm, the proportion of finer excipient in the total quantity of excipient being 1 to 20%. According to the invention, inhalable powders which contain 0.05 to 0.64%, more preferably 0.16 to 0.4% tiotropium bromide, are preferred.

If anhydrous crystalline tiotropium bromide is included in the inhalable powders mentioned above, these powder mixtures preferably contain 0.0012–2.41% of tiotropium bromide anhydrate. Also preferred are inhalable powders which contain between 0.048 and 0.96% of tiotropium bromide anhydrate. Of particular interest according to the invention are inhalable powders which contain 0.096 to 0.77%, more preferably 0.19 to 0.48% tiotropium bromide anhydrate.

The percentages mentioned within the scope of the present invention are always percent by weight.

An alternative, equally preferred embodiment for preparing inhalable powders containing tiotropium bromide anhydrate may also be prepared from inhalable powders formulated on the basis of the crystalline tiotropium bromide monohydrate. These contain between 0.0012 and 2.5%, preferably 0.05 to 1%, preferably 0.1 to 0.8%, more preferably 0.2 to 0.5% crystalline tiotropium bromide monohy-

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drate. The two components are preferably added through a screening granulator with a mesh size of 0.1 to 2 mm, most preferably 0.3 to 1 mm, even more preferably 0.3 to 0.6 mm. Preferably the coarser excipient is put in first and then the finer excipient fraction is added to the mixing container. In this mixing process the two components are preferably added batchwise, with half the coarser excipient being put in first followed by finer and coarser excipient added alternately. It is particularly preferable when preparing the excipient mixture to screen the two components in alternate layers. Preferably this screening of the two components takes place in 15 to 45, more preferably in 20 to 40 alternate layers. The mixing of the two excipients may take place while the two components are being added. However, it is preferably not done until the layers of ingredients have been added.

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The percentages mentioned within the scope of the present invention are always percent by weight.

An alternative, equally preferred embodiment for preparing inhalable powders containing tiotropium bromide anhydrate may also be prepared from inhalable powders formulated on the basis of the crystalline tiotropium bromide monohydrate. These contain between 0.0012 and 2.5%, preferably 0.05 to 1%, preferably 0.1 to 0.8%, more preferably 0.2 to 0.5% crystalline tiotropium bromide monohy-

Thus it is very clear that the instant claims recite an obvious variation of an old composition, a variation that was known in this very narrow field of anticholinergic agents. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a variation on the composition of Zirkle et. al. A person of ordinary skill in the art would have been motivated to do so based on the teaching of Gillett et. al. showing that inhalable administration was a good route for the administration of anticholinergics. Moreover the preparation of such a composition would be trivial to prepare as per U.S. patent 6,608,055.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 6-16 are rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;

> ***(F) The amount of direction provided by the inventor;***
> ***(G) The existence of working examples; and***
> **(H) The quantity of experimentation needed to make or use the invention**

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) The breadth of the claims: The claims are broad and drawn to many conditions, respiratory and otherwise but that's not really the main concern here, the main concern its that these compounds have not been shown to be useful for treating any disease. **(B) The nature of the invention:** This invention is drawn towards a method for treating diseases. **(D) The level of one of ordinary skill:** One of ordinary skill in the art of treating diseases or determining which drug to use for the treatment of a condition would be either a medical doctor or Pharm D. **(C) The state of the prior art:** While Zirkle states that these compounds are the preferred compounds of his study, and effective *in vitro* as anti-cholinergics (ibid. pg. 352-353), we don't know how these compounds behave *in vivo*.

(F) The amount of direction provided by the inventor and (G) the existence of working examples: While the applicant has provided descriptions of assays in the specification, and statements like "All data is given as mean +- standard error of the mean…"(pg. 7), the examiner cannot find the data in the specification. Statements like the one found on pg 9 line 14 "This experiment allows for the determination of duration of activity of the administered compound…" without actually providing a single piece of data lead the examiner to believe that these are mere recitations of possible experiments that could be performed with the compounds and that none were actually performed. No working examples exist. It is true as the applicant has pointed out that no requirement exists for in-vivo data, however only if some clear correlation exists between the in-vitro assay and the disease state. In fact in the instant case we have no in vitro assay? What is the in-vitro assay that was performed? Clearly one can come up with prophetic assays,

that do little to ease the unpredictable nature of these experiments as delineated below. This is called a research proposal. The specification seems to be a proposal for research to be conducted to find out if the compounds are useful for treating various disorders. **(E) The level of predictability in the art and (H) the quantity of experimentation needed to make or use the invention:** In the absence of this data we are left with an old compound that is an anticholinergic, however it is well known that there are many muscarinic receptor sub-types and even before the application was filed a review article (Lee, A.M. et. al. *Current Opinion in Pharmacology* **2001**, *1*, 223-229) tells us that at least five distinct subtypes of muscarinic receptor exist (M1-M5 in humans). Each one of these GPCRs has distinct tissue distribution, second-messengers and most-importantly ligand profile. All that we currently know about these compounds is that they inhibit the action of acetylcholine in a non-specific assay (given in 1962 the subtypes of muscarinic receptors were not known). Maybe these were organ bath assays with sheep vas deferens, pig heart or guinea pig ileum. We don't know, but it would be helpful to know the tissue type and animal. Even if we know the tissue type these receptors are of course GPCRs and the differences between the animal protein and those found in humans is sometimes substantial (more or less subtypes, or little homology). What creatures will be treated with these compounds? It was well known at the time of the invention that in order to be used in applicants claimed manner (a disease, and specifically a lung disease like COPD and asthma, claims 7-12), that the sub-type selectivity is very significant parameter to be determined in assessing the *potential* therapeutic benefit of a putative pharmaceutical. Lee, A.M. et. al. ibid. state on pg. 225:

> Nonselective muscarinic receptor antagonists
> Atropine, ipratropium and oxitropium are nonselective

> antimuscarinic drugs that successfully abrogate bronchoconstriction and airway hyperreactivity in humans; however, they bind M2 and M3 muscarinic receptors with equal affinity [5]. Since the M2 subtype is an inhibitory prejunctional autoreceptor, blocking the M2 muscarinic receptor with a nonselective antagonist increases acetylcholine release and **may enhance bronchoconstriction.** Ipratropium (Boehringer Ingelheim Pharmaceuticals Inc., California, USA) is the most widely used anticholinergic medication for airway disease. In guinea pigs, although it prevents bronchoconstriction in doses above 10 μg/kg (intravenous), it doubles vagally stimulated bronchoconstriction at lower doses. [48]. Paradoxical bronchoconstriction to ipratropium has been reported in humans [49,50], although no systematic study of M2 receptor blockade has been performed. Thus, the clinical efficacy of anticholinergics probably depends on the balance between M2 and M3 muscarinic receptor antagonism.

Thus we need to know several things: 1) Do these compounds antagonize muscarinic receptor subtypes found in the lungs? 2) What is the selectivity for receptor subtypes? 3) Are the effects *in vitro* correlated with *in vivo* activity? Number three is perhaps the most important factor, given the complexity of receptor sub-types, the possibly different affinities, rates of dissociation, etc. The real question is does it work as a therapy in a creature? Again it must be reiterated that applicant has provided absolutely no data for these compounds, although Smith-Kline French may have acquired such data, it has apparently not been published. Since no data is given we cannot begin to evaluate these compounds as drugs, hence any claim directed towards inhalant formulations cannot be evaluated. It is also noted that no such formulations have been prepared and applicant has simply listed a laundry list of possibilities. We are provided with no answers to the questions above, thus it is very clear that one could not use this invention that has no working examples in this unpredictable art without undue experimentation. In regards to claim 6

which is drawn to "inhibiting the binding of acetylcholine to a[sic] acetylcholine receptor in a mammal in need thereof", we do not know what mammals need this compound since no physiological outcome has been associated with administering these compounds, thus no veterinarian or physician would know which mammals should receive this material and the method cannot be practiced. Since no "pharmaceutical" use is shown, then the composition claims 1-4 are not enabled for pharmaceutical use.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

9. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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